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A REVIEW ON SPECTROPHOTOMETRIC AND CHROMATOGRAPHIC METHODS FOR THE ESTIMATION OF PHENYLEPHRINE IN BULK AND DIFFERENT DOSAGE FORMS

A. Geetha Susmita*, G. Rajitha and T. Lakshmi Bhavani

Institute of Pharmaceutical Technology
Sri Padmavati Mahila Visvavidyalayam (Women's University), Tirupati-517502, Andhra Pradesh, India.

***Corresponding author E-mail**: susmithaadepu@gmail.com

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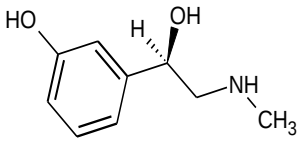
ABSTRACT

Phenylephrine hydrochloride is used as nasal decongestant. Oral phenylephrine is extensively metabolized by MAO enzyme in the gastrointestinal tract and liver. It is a direct selective alpha adrenergic receptor agonist; it does not cause release of endogenous noradrenalin, as pseudoephedrine does. Phenylephrine hydrochloride (alpha-adrenergic, sympathomimetic agent) is a useful vasoconstrictor of sustained action with little effect on the myocardium or the central nervous system. Phenylephrine is rarely used to increase the blood pressure as a vasopressor in unstable patients with hypotension. It is available in the following dosage forms: nasal drops, nasal spray, eye drops and phenylephrine injection. Phenylephrine is also available as oral tablets, chewable tablets, oral disintegrating tablets, capsules, suspensions and sachets formulations. This review shows different methods developed for the determination of Phenylephrine and along with combinations like UV-spectroscopy and liquid chromatography.

INTRODUCTION:

Phenylephrine is 3-[(1R)-1-hydroxy-2- (methyl amino) ethyl] phenol, appears as a white or almost white, crystalline powder. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. The Phenylephrine is a base with a pKa value of 8.97 and melts about 174°C.[1,2] It is used as a sympathomimetic amine that acts predominantly on α-adrenergic receptors. Phenylephrine is official in IP, BP, EP and USPNF pharmacopoeia[3]. It is mainly used to treat nasal congestion, but may also be useful in treating hypotension and shock, hypotension during spinal anesthesia, prolongation of spinal anesthesia, paroxysmal supraventricular tachycardia, symptomatic relief of external or internal haemorrhoids and to increase blood pressure as an aid in the diagnosis of heart murmurs.

Figure 1: Structure of Phenylephrine



Molecular Formula: $C_9H_{13}NO_2$

Table 1: Analysis of Phenylephrine by using UV-spectroscopy and chromatography techniques

S.No.	DRUG	METHOD	DESCRIPTION	Ref.no.
1	Phenylephrine Hydrochloride in pharmaceutical nasal drops formulations.	UV-Spectrophotometry	Wavelength: 291nm Diluent: sodium hydroxide (pH13.5) Linearity Range: 10 – 100µg·cm^{-3} Correlation Coefficient (r^2): 0.9990. LOD and LOQ: 0.892µg·cm^{-3} and 2.969 µg·cm^{-3}	5
2	Bromhexine Hydrochloride and Phenylephrine Hydrochloride in their Combined Pharmaceutical Dosage Form	UV-Spectrophotometry	Wavelength: 241nm for Phenylephrine HCl & 233nm for Bromohexine HCl Solvent: Methanol, Linearity Range: 5-30µg/ml for BromhexineHCl and 10-60 µg/ml for Phenylephrine HCl Correlation Coefficient (r^2): 0.999 for Bromhexine HCl and 0.998 for Phenylephrine HCl LOD and LOQ: 0.0015 & 0.2330 µg/ml for Bromhexine HCl and 0.002 & 0.2858 µg/ml for Phenylephrine HCl	6
3	Ebastine and Phenylephrine Hydrochloride in combined Tablet dosage Form	UV-Spectrophotometry	Wavelength: 231.61nm Ebastine & 242.21nm for Phenylephrine HCl Solvent: Methanol, Linearity Range:5-40µg/ml for both Correlation Coefficient(r^2): 0.9996 for Ebastine and 0.9991 for Phenylephrine HCl LOD and LOQ: 0.84µg/ml and 2.54 µg/ml for Ebastine LOD and LOQ: 0.94µg/ml and 2.85 µg/ml for Phenylephrine Hydrochloride	7
4.	Chlorpheniramine Maleate and Phenylephrine Hydrochloride in Bulk and Capsule Dosage Form	UV-Spectrophotometry	Wavelength: 261nm for Chlorpheniramine Maleate &272nm for Phenylephrine HCl. Linearity Range:2-12µg/ml for Chlorpheniramine Maleate and 5-30 µg/ml for Phenylephrine Hydrochloride Correlation Coefficient(r^2): 0.9991 for Chlorpheniramine Maleate and 0.9994 for Phenylephrine HCl LOD and LOQ: 0.115µg/ml and 0.348 µg/ml for	8

			Chlorpheniramine Maleate LOD and LOQ: 0.200µg/ml and 0.608µg/ml for Phenylephrine Hydrochloride.	
5	Phenylephrine, Dimethindine Maleate and its major toxic impurity; 2-ethyl pyridine, in raw material and nasal gel	TLC	Stationary phase: Silica Gel TLC F254 plates Mobile phase: toluene: Acetone: isopropyl alcohol: ammonia (5.3:2.7:1.8:0.4,by volume) Retention factor(R_f): 0.26 ±0.01 for Phenylephrine 0.54 ± 0.02 for Dimethindine Maleate. 0.72 ± 0.01 for 2-ethyl pyridine, Correlation coefficient (r^2): 0.9990 for Phenylephrine, 0.9990 for Dimethindine Maleate and 0.9994 for 2-ethyl pyridine.	9
6	Paracetamol, Phenylephrine hydrochloride, Nimesulide, Cetrizine and Caffeine in bulk and pharmaceutical dosage form	HPTLC	Stationary phase: Merck aluminum plates precoated with silica gel 60 F_{254}. Mobile phase: Toluene: Ethyl acetate: Methanol: Formic acid (16:2:4:0.8, v/v/v/v). Retardation factor: Paracetamol (0.37), Phenylephrine hydrochloride (0.09), Nimesulide (0.70), Cetrizine (0.27) and Caffeine (0.51). Wave length: 212 nm. Linearity range: 200-1400 ng $band^{-1}$ for Paracetamol, Nimesulide, Cetrizine, Caffeine and 100-1400 ng $band^{-1}$ for Phenylephrine hydrochloride.	10
7	Two Binary Mixtures Containing Ketorolac Tromethamine (KTC) with Phenylephrine Hydrochloride (PHE) and with Febuxostat (FBX) in bulk drug and in combined dosage forms.	HPTLC	Stationary phase: Merck HPTLC aluminum sheets of silica gel 60 F254 Mobile phase: Chloroform methanol–ammonia (7:3:0.1, v/v) and (7.5:2.5:0.1, v/v) for KTC/PHE and KTC/FBX mixtures, respectively. Wave length: 273 and 320 nm for Mixtures 1 and 2, respectively. Linearity range: 0.20–0.60 and 0.60–1.95 µg $band^{-1}$ for KTC and PHE (Mixture 1), respectively, and	11

			0.10–1.00and 0.25–2.50 µg band^{-1} for KTC and FBX (Mixture 2), respectively. Correlation coefficient (r^2) : > 0.999.	
8	Ascorbic acid, Phenylephrine, Paracetamol and Caffeine in tablet	HPLC	Mobile Phase: Acetonitrile and Phosphate buffer (pH 6.50) (10 : 90, v/v). Stationary Phase: monolithic column, Onyx Monolithic C18 (100 x 4.6 mm) Flow Rate: 1.0 ml/min Wavelength: 210 nm (Phenylephrine, Paracetamol) 235 nm (Ascorbic acid and Caffeine) Linearity Range: 50 150µg/ml. Retention time: Correlation Coefficient (r^2): 0.9992 for ascorbic acid, 0.9994 for phenylephrine, 0.9999 for paracetamol and 0.9992 for caffeine.	12
9	Bromhexine and phenylephrine HCl in its Pharmaceutical combined dosage form	RP-HPLC	Mobile Phase: Buffer (pH 5.0)-Acetonitrile-Triethylamine (80:20:0.25). Stationary Phase: C18 column (25 cm × 0.46 cm) Hypersil BDS. Flow Rate: 1.0 ml/min. Linearity Range: 4-12µg/ml for Bromhexine and 5-15µg/ml for Phenylephrine HCl. Wavelength: 225nm Retention time: Bromhexine and Phenylephrine HCl were found to 3.66min and 5.29min respectively. Correlation Coefficient (r^2): 0.99 for Bromhexine HCl and 0.99 for Phenylephrine HCl	13
10	Ebastine and Phenylephrine hydrochloride in tablet dosage form	RP-HPLC	Mobile Phase: Buffer: Acetonitrile (20 : 80) % v/v Stationary Phase: Inertsil ODS-3 (250 mm × 4.6 mm i.d. 5 µm particle size). Flow Rate: 0.5 ml/min. Wavelength:230nm Linearity Range: 50-100µg/ml Retention Time: henylephrine hydrochloride and Ebastine was 3.90 min and 5.83 min respectively. Correlation Coefficient (r^2): 0.998 for Phenylephrine hydrochloride	14

			and 0.999 for Ebastine. LOD: 0.352µg/ml for Phenylephrine hydrochloride and 0.248 µg/mL for Ebastine. LOQ: 1.068µg/mL for Phenylephrine hydrochloride and 0.752µg/mL for Ebastine.	
11	Phenylephrine hydrochloride and Chlorpheniramine maleate in pharmaceutical dosage form	RP-HPLC	Mobile phase: 0.01M phosphate buffer: acetonitrile (70: 30). Stationary Phase: Princeton C8 analytical column (250 x 4.6mm, 5µm) Flow Rate:1ml/min Wavelength: 230nm Linearity Range:5-60 µg/mL Correlation Coefficient (r^2): 0.9996 for Phenylephrine hydrochloride and 0.9998 for Chlorpheniramine maleate. LOD: 0.28 µg/mL for phenylephrine hydrochloride and 0.36 µg/mL for Chlorpheniramine maleate. LOQ: 0.86 µg/mL for phenylephrine hydrochloride and 1.1µg/mL for Chlorpheniramine maleate.	15
12	Ebastine and phenylephrine hydrochloride in tablet	RP-HPLC	Mobile phase: MeOH:KH_2PO_4(80:20 pH 5.5) Stationary Phase: Prontosil C18 [4.6(id) × 250mm] Flow Rate: 1.5ml/min Wavelength: 275nm Solvent: Methanol Retention Time: 3.5 min for ebastine and 1.8 min for phenylephrine HCl	16
13	Phenylephrine HCl and CetrizineHCl in Tablet dosage form	RP-HPLC	Mobile Phase: Buffer (0.1 M Ammonium dihydrogen phosphate pH 5.2 ± 0.05) : Acetonitrile (50:50% v/v) Stationary Phase: Princeton SPHER C18 column (250 mm x 4.6 mm id, 5 µ particle size) Flow Rate: 1.0ml/min Wavelength: 225nm, Linearity Range: 10-60µg/ml for Phenylephrine hydrochloride and 5-30µg/ml for Cetrizine	17

			HCl. Retention Time:2.19 ± 0.05 min for phenylephrine hydrochloride and 4.16 ± 0.05 min for CetrizineHCl Correlation Coefficient (r^2): 0.9998 for both.	
14	Tropicamide and Phenylephrine Hydrocholride in ophthalmic formulation	RP-HPLC	Mobile Phase: Buffer (0.05M KH2PO4, pH-4) and methanol in the ratio of 60:40 v/v. Stationary Phase: ODS Hypersil C18, 250mm × 4.6mm, 5µ (Particle Size) column. Flow Rate: 1.0 ml/min Wavelength: 216nm Retention Time: 3.290 min for Tropicamide and 5.063 min for Phenylephrine Hydrochloride Correlation Coefficient (r^2): 0.999 for Tropicamide and 0.998 for Phenylephrine Hydrocholride. Linearity Range: 4-12µg/ml for Tropicamide and 25-70 µg/ml for Phenylephrine Hcl	18
15	Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride And Triprolidine Hydrochloride In Bulk And Combined Tablets Dosage Forms	RP-HPLC-PDA	Mobile Phase: Methanol:acetonitrile: 0.1M potassium dihydrogen phosphate buffer (75:15:10) adjusted to pH 6.8with sodium hydroxide. Stationary Phase: Kromasil C18 (250 × 4.6mm, 5µm) Flow Rate:1.0 ml/min Wavelength: 271nm Linearity Range: Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride and Triprolidine Hydrochloride were 48 - 112, 24 – 56 and 16-14 mcg/ml, respectively. Retention Time: Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride and Triprolidine Hydrochloride were measured at 2.547, 3.783 and 6.017 min, respectively. Correlation Coefficient (r^2): Dextromethorphan - 0.999 Phenylephrine Hydrochloride - 0.998. Triprolidine	19

			Hydrochloride - 0.997	
16	Ketorolac Tromethamine And Phenylephrine in Pharmaceutical Dosage Form	RP-HPLC-PDA	Mobile Phase: Phosphate Buffer (pH 3.0): Acetonitrile (60:40), Stationary Phase: Zodiac, C18 (150×4.6× 5µm) Flow Rate: 1.0 ml/min, Wavelength: 303nm, Linearity Range: 36-84µg/ml for ketorolac tromethamine and 60-140 µg/ml for phenylephrine. Retention Time: 4.1 min. for ketorolac tromethamine and 2.9 min. for phenylephrine. Correlation Coefficient (r^2): 0.9995 for ketorolac tromethamine and 0.9996 for phenylephrine. LOD: 0.75µg/ml for ketorolac tromethamine and 1.89µg/ml for phenylephrine LOQ: 2.29µg/ml for ketorolac tromethamine and 5.73µg/ml for phenylephrine	20
17	Phenylephrine And Ketorolac In Injectable Preparations	RP-HPLC-PDA	Mobile Phase: Buffer and Acetonitrile (30:70). Stationary Phase: Std BDS C8column (250mm × 4.6 mm id,5µm particle size) Flow Rate: 1 ml/min, Wavelength: 220nm Retention Time: 2.313min for Phenylephrine Hydrochloride and 3.090min for Ketorolac. Correlation Coefficient (r^2): 0.9992 for phenylephrine and 0.9994 for ketorolac Linearity Range: 20-120µg/ml for Phenylephrine and 6-36µg/ml for ketorolac.	21
18	Phenylephrine hydrochloride and Guaifenesin in bulk drug and pharmaceutical dosage form	RP-HPLC-PDA	Mobile Phase: 5Mm ammonium acetate: acetonitrile (80:20 v/v), Stationary Phase: A Zorbax reverse phase C18 column(150 × 3.0mm, 3.5µm) Flow Rate: 1ml/min, Wavelength: 222nm Linearity Range: 1-5µg/ml for Phenylephrine hydrochloride and 15-75µg/ml for Guaifenesin. Retention Time: 1.62 min for phenylephrine	22

			hydrochloride and 2.28min for guaifenesin. Correlation Coefficient (r^2): > 0.999. LOD: 0.11 µg/mL for Phenylephrine hydrochloride and 0.08 µg/mL for Guaifenesin.LOQ: 0.34 µg/mL for Phenylephrine hydrochloride and 0.26 µg/mL for Guaifenesin.	
19	Acetaminophen, Phenylephrine Hydrochloride and Dextromethorphan Hydrobromide in Liquicap Dosage form	RP-HPLC with Gradient programme	Stationary Phase: Inertsil C18 column (250 × 4.6mm, 5µm) Mobile phase: The composition of mobile phase A (90:10) buffer: acetonitrile and mobile phase B (50:50) buffer: acetonitrile. Timed gradient programme time/A% is 0.0/100, 6.0/100, 6.5/85, 16.0/0, 16.5/100, 20.0/100. Flow Rate: 1.5ml/min Wavelength: 272nm, Retention Time: Acetaminophen - 5min. Phenylephrine hydrochloride - 3min. Dextromethorphan hydrobromide -15min. Correlation Coefficient (r^2): Acetaminophen - 0.9999 Dextromethorphan Hydrobromide-0.9998 Phenylephrine Hydrochloride - 0.9999	23
20	Phenylephrine, Acetaminophen, Guaifenesin and Dextromethorphan in tablet dosage form	RP-HPLC with Gradient programme	Stationary Phase: C18 column Altima (150 x 4.6 mm, 5µ) Mobile phase: Orthophosphoric acid in a 1000ml of water as Solvent A and Acetonitrile as Solvent B Timed gradient programme time/A% is 0/88, 3/88, 10/15, 10.5/88, 13/88. Flow Rate: 1.0ml/min. Wavelength: 272nm. Linearity Range: Phenylephrine - 2.0-7.0µg/mL, Acetaminophen – 130-455µg/mL, Guaifenesin 50-300µg/mL and Dextromethorphan 2.5-15 µg/mL respectively.	24

Phenylephrine is also used to treat sinus congestion, or congestion of the tubes that drain fluid from your inner ears, called the Eustachian.[4] This paper focuses on the review of available methods for the analysis of phenylephrine. The literature survey reported several analytical methods for the determination of Phenylephrine, which include UV- spectrophotometry, Thin Layer Chromatography (TLC), High Pressure Thin Layer Chromatography (HPTLC), High Performance Liquid Chromatography (HPLC), Reverse Phase-HPLC (RP-HPLC) in bulk and different dosage forms.

CONCLUSION:

This review specifies the reported spectroscopic and chromatographic methods developed and validated for the estimation of Phenylephrine and along with different combination drugs. Rendering to this review it was concluded that for the analysis of phenylephrine, different spectroscopic and chromatographic methods are available for single component as well as for different combinations. It was found that the Mobile phase containing Acetonitrile, methanol, phosphate buffer were common for most of the chromatographic methods for faster elution. The flow rate was found to be in the range 0.5-1.5ml/min for the shorter retention time. Methanol was used as a common solvent in most of the spectroscopic and chromatographic methods.

All these methods were found to be simple, economic, accurate, reproducible and precise in nature. Most of the methods were of UV absorbance detection and RP-HPLC as these methods offer best available reliability, repeatability, analysis time and sensitivity. In future, there is a scope for the development of validated hyphenated methods for the estimation of Phenylephrine and combination with other drugs in the biological fluids.

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